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EP 0600517 A1
Tetrahedron Lett. (1994), 35(43), 7893-6 Bioorg. Med. Chem. Lett. (1994), 4(18), 2223-8

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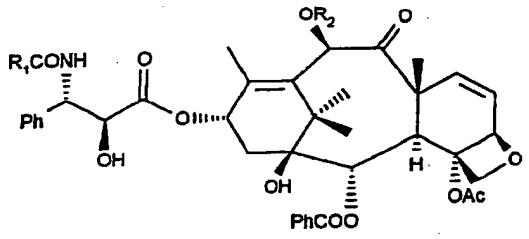
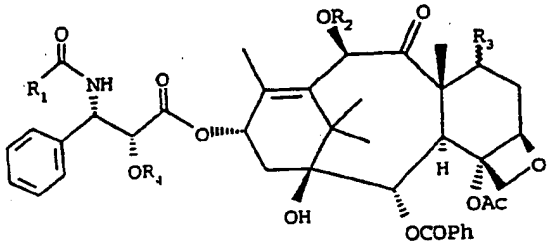
(54) Taxane derivatives

(57) Taxane derivatives modified at 6 - 7 positions of the taxane derivative skeleton (taxol numbering) of formula Ia:



Ia

wherein R_1 represents OR or R wherein R is C_1-C_5 alkyl, C_2-C_5 alkenyl or C_6-C_{10} aryl and R_2 represents H or CH_3CO, are endowed with antitumor activity. The compounds of formula Ia and their epimers at 2'position are prepared from a compound of formula II



II

wherein R_3 is a leaving group and R_4 is a hydroxy protecting group. Compounds of formula II are novel when R_3 is CH_3SO_2O or CF_3SO_2O in the alpha-configuration and also have antitumour activity.

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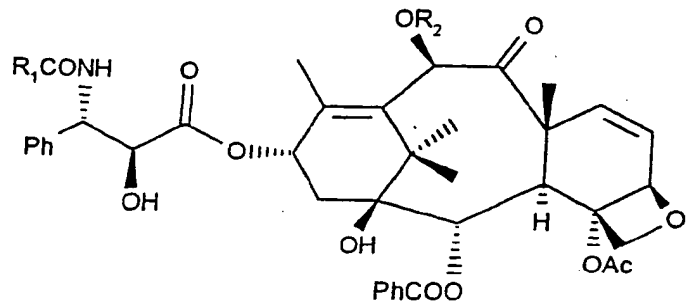
UNSATURATED TAXANE COMPOUNDS

The present invention is directed to taxane derivatives endowed with antitumor activity, to a process for their preparation and to pharmaceutical compositions containing them.

The taxane family of diterpenes includes Paclitaxel (also named taxol in several publications), isolated and characterized from an extract of bark of Taxus brevifolia L., and Cephalomannine (see J. Chem. Soc. Chem. Comm. 102, 1979); other taxane analogues are also known and were prepared by semisynthesis starting from 10-deacetyl baccatin III, extracted from the needles of Taxus baccata L. (see Wani et al., J. Am. Chem. Soc. 93, 2325 , 1971; Lovelle et al., Proc. Am. Assoc. Cancer Res. 31, 417, 1990).

Particularly, taxol is a very potent anticancer drug and is already applied with success to the treatment of platinum-resistant ovarian cancer. Nevertheless there is a continuous need for more potent compounds having the broadest possible spectrum of activity on different cancer types.

The present invention provides taxane derivatives modified at the 6-7 positions of the taxane skeleton (taxol numbering). More especially, the invention provides 2'epi taxane derivatives of the formula Ia:



Ia

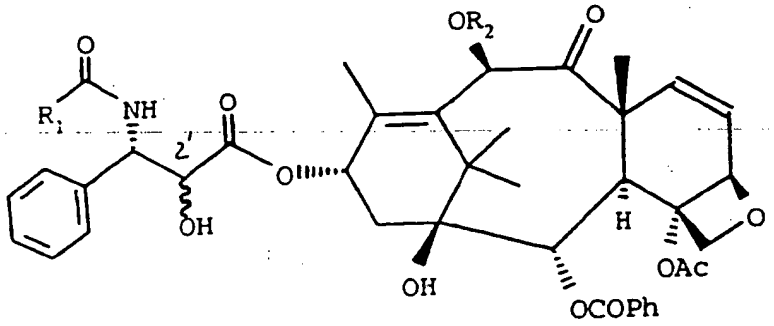
wherein R_1 represents OR or R wherein R is C_1-C_5 alkyl, C_2-C_5 alkenyl or C_6-C_{10} aryl and R_2 represents H or Ac (CH_3CO). The hydroxy group at 2′-position is in the β configuration.

The alkyl and alkenyl groups may be straight chain groups or branched chain groups. A C_1-C_5 alkyl group may be methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl or n-pentyl. A C_2-C_5 alkenyl group may be ethenyl, propenyl, 1-methyl-1-propenyl or butenyl. A C_6-C_{10} aryl group may be phenyl or naphthyl, for example α-naphthyl or β-naphthyl. Preferably, R_1 represents phenyl, tertbutoxy (t-ButO), 1-methyl-1-propenyl or n-pentyl. A preferred compound of the invention is 7-deoxy-taxol-6-ene.

The present invention also provides a process for the preparation of taxane derivatives of formula Ia and their epimers at 2′ position. In fact structures of formula Ia can be obtained by an elimination process from a taxane derivative with a suitable leaving group at the 7-position (like triflate, mesylate, etc.) and with a proper protecting group at the 2′-position (like the acetyl group).

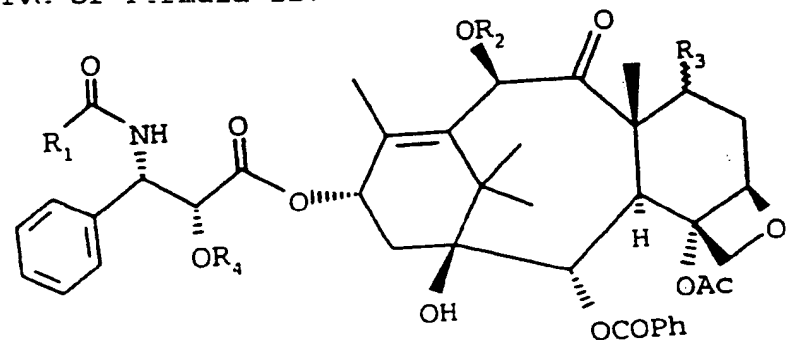
The compounds of formula I are endowed also with antitumor activity.

Accordingly, the present invention provides a process for preparing a taxane derivative of formula I



I

wherein R_1, R_2 are as defined above, the process comprising carrying out an elimination reaction on a protected taxane derivative of formula II:



II

wherein R_1 and R_2 are as defined above, R_3 is a leaving group and R_4 is a hydroxy protecting group, thereby to form a said taxane derivative of formula I wherein the 2′-hydroxy group carries a said hydroxy protecting group R_4; and carrying out the following steps in any order:

a) separating the resulting isomers which are in the α and β configuration at the 2′-position; and

b) removing the said hydroxy protecting group R_4.

Particularly, the compounds of formula Ia according to the

present invention are obtained by separating the desired isomer in the β cofiguration.

The leaving group R_3 can therefore be CH_3SO_2O-, CF_3SO_2O- or another suitable leaving group. R_4 may be Ac, $-OCOCH_2Ph$, $-OCOCH_2CH=CH_2$, $(i-Pr)_3Si-$, $t-BuMe_2Si-$, $t-BuPh_2Si-$ or another suitable hydroxy protecting group. The wavy line denotes that the R_3 group linked at the 7-position of the taxane structure may be in the α or β configuration.

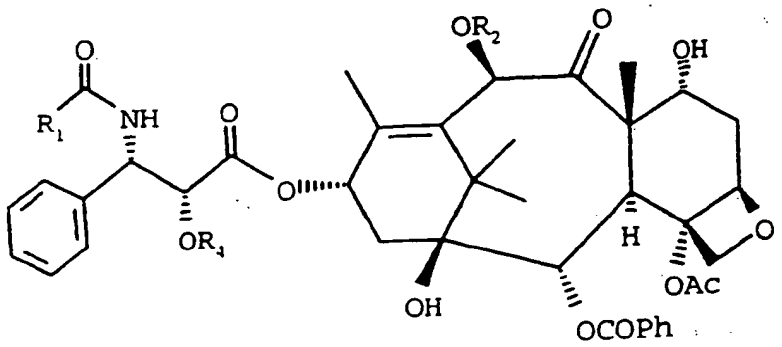
The elimination reaction is typically achieved by reacting a compound of formula II with a base. The elimination reaction may thus be performed in the presence of a base such as MeSM, MN_3, MCN, M_2CO_3, AcOM, etc (wherein M represents an alkali metal such as Na or K either in a suitable polar aprotic organic solvent like dimethylformamide, dimethylsulfoxide, CH_3CN, etc. or under phase transfer catalysis conditions in the presence of a quaternary ammonium salt (for example $n-Bu_4NHSO_4$) and in an apolar organic solvent (for example toluene, benzene, methylene chloride, chloroform, etc). The reaction temperature may vary from 0°C to 120°C, for example from 0 to 30°C.

The removal of the hydroxy protecting group R_4 can be carried out under standard conditions such as hydrolysis or hydrogenolysis or utilising tetrabutylammonium fluoride for silyl groups. When the protecting group is Ac, it may be removed by treatment with sodium bicarbonate in MeOH : H_2O as reaction medium or with diethylamine in methanol. Removal of

the hydroxy protecting group R_4 yields compounds of formula I. The separation of the isomers which are α and β at the 2′-position may be carried out by analogy with known methods. Preferably, the separation is carried out after removal of R_4 protecting group. The separation may be carried out by means of liquid chromatography, preferably on silica gel.

Taxane derivatives of formula II wherein R_3 is either CH_3SO_2O- or CF_3SO_2O- in the α configuration are novel and form part of the invention.

These taxane derivatives according to the invention can be obtained reacting a compound of formula III:



III

wherein R_1, R_2 and R_4 are as defined, above with a compound of formula IV :

$$CX_3SO_2-Y \qquad \text{IV}$$

wherein X is H or F and Y is a leaving group. The leaving group Y may be halogen (e.g. Cl) or $-OSO_2CX_3$ or another suitable leaving group.

Compounds of formula II in fact can be generally obtained by reacting compounds of formulae III having the hydroxy group at 7 position in α or β configuration and IV in the presence of a base (for example pyridine, dimethylaminopyridine, diisopropylethylamine, etc) in a suitable organic solvent which can be pyridine itself, CH_3CN, CH_2Cl_2, etc. The reaction temperature may vary from room temperature to 70°C. The reaction time may vary from 1 to 12hrs.

Compounds of formula III practically are taxane derivatives with a 2'-hydroxy protecting group. Several examples are already known in the literature. For instance the compound of formula III where R_1 is phenyl, R_2 and R_4 are both Ac and the 7-OH configuration is β (i.e. 2'-acetyltaxol) is described in Bioch. Bioph. Res. Comm. 124, 329 (1984). The compound of formula III where R_1 is phenyl, R_2 is Ac, R_4 is $-OCOCH_2Ph$ and the 7-OH configuration is β is reported in Tetrah. 49, 2805 (1993) and the same compound where the 7-OH configuration is α is reported in Tetrah. Lett. 34, 6845 (1993).

Analogously the compound of formula III wherein R_1 is phenyl, R_2 and R_4 are both Ac and the 7-OH configuration is α (i.e. 2'-acetyl-7-epitaxol) may be obtained, starting from 7-epitaxol already known in the literature (see J. Nat. Prod. 49, 665-9 (1986)). Other compounds of formula III are known compounds or may be prepared by known methods from known compounds, see for example WO9323389-A.

BIOLOGICAL ACTIVITY

The cytotoxic activity of the compounds has been evaluated on B16-F10 murine melanoma cell line which was responsive to taxol and on UV2237 murine fibrosarcoma cell line which was less responsive to taxol (A). The mode of action of the compound was also tested on the tubulin assembly-disassembly assay in comparison with taxol (B).

(A) In vitro drug sensitivity assay

Exponentially growing B16-F10 murine melanoma cells were seeded ($2x10^4$/ml) in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum and 2 mM glutamine in 24-well plates (Costar). Exponentially growing UV2237 murine fibrosarcoma cells were seeded ($2x10^4$/ml) in E-MEM medium with non-essential aminoacids and Na-pyruvate supplemented with 1% vitamins, 2mM glutamine and 10% heat-inactivated fetal calf serum in 24-well plates (Costar). Scaled concentrations of tested compounds were added immediately after seeding.

The inhibition of cell growth was evaluated by counting cells with a Coulter counter after 24hrs incubation. For each tested compound concentration triplicate cultures were used. The antiproliferative activity of the tested compounds was calculated from dose-response curves and expressed as IC_{50} (dose causing 50% inhibition cell growth in treated cultures relative to untreated controls). The results are shown in Table I.

(B) Microtubule assembly and disassembly assay

Calf brain tubulin was prepared by two cycles of assembly-disassembly (Shelanski M.L., Gaskin F. and Cantor C.R., Proc. Natl. Acad. Sci. U.S.A. 70, 765-768, 1973) and stored in liquid nitrogen in MAB (0.1 M MES, 2.5 mM EGTA, 0.5 mM $MgSO_4$ 0.1 mM EDTA, 0.1 mM DTT pH 6.4). All the experiments were carried out on protein stored for less than 4 weeks. Before each experiment, the tubulin was kept 30 min at 4°C. Assembly was monitored by the method of Gaskin et al. (Gaskin F., Cantor C.R. and Shelanski M.L., J. Molec. Biol. 89, 737-758, 1974).

The cuvette (1 cm path) containing tubulin (1mg/ml) and 1 mM GTP was shifted to 37°C and continuous turbidity measurements were made at 340 nm on a Perkin-Elmer 557 double wavelength double beam spectrophotometer equipped with an automatic recorder and a thermostatically regulated sample chamber. After 30 minutes, 4 mM $CaCl_2$ was added and depolymerisation was measured for 10 minutes as decreased turbidity. At regular intervals of 15 minutes scaled doses of the tested compounds were added and variations in the turbidity were monitored. Data are expressed as percentage of repolymerisation induced by the tested compounds. The results are shown in Table I.

TABLE 1				
	(B) Tubulin Assembly (%)		(A) Cytotoxicity	
	dose: 0.5γM	5γM	IC_{50}(nM) BI6F10	UV2237
Compound prepared in Example 4	24	66	4 ± 1	5 ± 2
Compound prepared in Example 5	21±4	100±5	40±6	249±41
Paclitaxel (reference compound)	39 ± 2	93 ± 3	36 ± 10	452 ± 78

The taxane derivatives of formulae Ia and II are thus antitumor agents. A human or animal suffering from a tumor may thus be treated by a method which comprises the administration thereto of an effective amount of a taxane derivative of formula Ia or II according to the invention. The condition of the human or animal may thereby be improved.

Examples of tumors that can be treated are sarcomas, carcinomas, lymphomas, neuroblastomas, melanomas, myelomas, Wilms tumor, leukemias and adenocarcinomas. The taxane derivatives of formulae Ia and II can be used to treat ovarian cancer, for example platinum-resistant ovarian cancer, metastatic breast cancer, non-small cell lung cancer, and head and neck cancer.

The invention also provides a pharmaceutical composition which comprises, as active ingredient, a compound of formula Ia or II according to the invention and a pharmaceutically acceptable carrier or diluent. The composition of the invention is usually prepared following conventional methods

and is administered in a pharmaceutically suitable form.

Administration can be made by any of the accepted ways for administration of antitumor agents such as intravenous, intramuscular or subcutaneous injection or topical application. For systemic injection the active compound may be, e.g. dissolved in a vehicle consisting polyoxyethylated castor oil (Cremaphor EL) 50% and ethanol 50% and then diluted with glucose 5% solution at the desired concentration, or other pharmaceutically suitable carriers.

The amount of the active compound administered depends on the treated subject, for example age, weight and sex; and the severity of the affliction. The method of administration depends on the judgement of the prescribing physician. A suitable dosage for an average 70 kg may range from about 0.01g to about 1g per day.

The following Examples illustrate the invention but they are not intended to limit it thereto. 7-Epitaxol was prepared according to a literature method (Tetrah. Lett. 34, 6845, 1993).

Example 1

2'-Acetyl-7-epitaxol

539mg (0.631 mmol) of 7-epitaxol in pyridine (4mL) under nitrogen were treated with acetic anhydride (295μL, 3.13 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1hr, then poured into ice-water and extracted twice with

ethyl acetate. The organic phase was washed once with 1N HCl, once with brine and then dried over sodium sulphate, filtered and evaporated under vacuum, yielding 539mg (95%) of the title compound as a white crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz) :

1.14 (s, 3H, CH_3-16)

1.18 (s, 3H, CH_3-17)

1.67 (s, 3H, CH_3-19)

1.77 (s, 1H, OH-1)

1.90 (d, J= 1.2 Hz, 3H, CH_3-18)

2.14, 2.19 (two singlets, 6H, CH_3CO-2'+ CH_3CO-10)

2.0 - 2.4 (m, 4H, CH_2-14 + CH_2-6)

2.54 (s, 3H, CH_3CO-4)

3.71 (ddd, J = 11.7 Hz, J = 5.0 Hz, J = 2.0 Hz, 1H, H-7)

3.93 (d, J = 7.5 Hz, 1H, H-3)

4.39 (s, 2H, CH_2-20)

4.70 (d, J = 11.7 Hz, 1H, OH-7)

4.94 (dd, J = 3.5 Hz, J = 9.1 Hz, 1H, H-5)

5.56 (d, J = 3.2 Hz, 1H, H-2')

5.76 (d, J = 7.5 Hz, 1H, H-2)

5.98 (dd, J = 3.2 Hz, J = 9.4 Hz, 1H, H-3')

6.22 (m, 1H, H-13)

6.82 (s, 1H, H-10)

6.90 (d, J = 9.4 Hz, 1H, NH)

7.3 - 8.2 (m, 15H, 3 Ph)

Example 2

2'-Acetyl-7-epi-methanesulphonyltaxol

To a solution of 404mg (0.451 mmol) of 2'-acetyl-7-epitaxol in pyridine (6mL) under nitrogen were added dimethylaminopyridine (55mg, 0.45 mmol) and, dropwise at 0°C, methanesulphonylchloride (882μL , 11.39 mmol). The reaction mixture was allowed to warm to room temperature and then heated at 50°C for 18hrs. The reaction mixture was poured into ice-water, extracted with ethyl acetate, the organic phase washed once with 1N HCl, with brine, dried over sodium sulphate, filtered and evaporated under vacuum. The crude mixture was purified by flash chromatography over silica gel (eluant : n-hexane/ethyl acetate = 1/1) yielding 298mg (68%) of the title compound as a white solid. 42.5mg (11%) of the starting material were recovered.

^{1}H NMR ($CDCl_3$, 400 MHz) :

1.16 (s, 3H, CH_3-16)

1.20 (s, 3H, CH_3-17)

1.77 (s, 3H, CH_3-19)

2.01 (d, J= 1.2 Hz, 3H, CH_3-18)

2.15, 2.19 (two singlets, 6H, CH_3CO-2 + CH_3CO-10)

2.1 - 2.3 (m, 2H, CH-14 + CH-6)

2.49 (s, 3H, CH_3CO-4)

2.51 (dd, J = 15.2 Hz, J = 9.4 Hz, 1H, CH-14)

3.08 (ddd, J = 16.4 Hz, J = 9.1 Hz, J = 2.9 Hz, 1H, CH-6)

3.25 (s, 3H, CH_3SO2-)

4.09 (d, J = 7.3 Hz, 1H, H-3)

4.33, 4.54 (two doublets, J = 8.5 Hz, 2H, CH_2-20)

4.70 (dd, J = 2.9 Hz, J = 2.9 Hz, 1H, H-7)

5.04 (dd, J = 5.6 Hz, J = 9.1 Hz, 1H, H-5)

5.54 (d, J = 2.9 Hz, 1H, H-2')

5.76 (d, J = 7.3 Hz, 1H, H-2)

6.01 (dd, J = 2.9 Hz, J = 9.4 Hz, 1H, H-3')

6.25 (m, 1H, H-13)

6.49 (s, 1H, H-10)

6.88 (d, J = 9.4 Hz, 1H, NH)

7.3 - 8.2 (m, 15H, 3 Ph)

Example 3

2'-Acetyl-7-deoxy-taxol-6-ene

To a solution of 2'-acetyl-7-epimethanesulphonyltaxol (391mg, 0.127 mmol) under nitrogen in N,N-dimethylformamide (8mL) was added sodium azide (330mg, 5.075 mmol). The reaction mixture was stirred at about 90°C for 5hrs, then treated with water and ethyl acetate. The organic phase was washed twice with water, once with brine, dried over sodium sulphate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography over silica gel (eluant:n-hexane/ethyl acetate = 1/1) yielding 128mg (36%) of the title compound.

^{1}H NMR (CDCl3, 400 MHz) :

1.14 (s, 3H, CH_3-16)

1.24 (s, 3H, CH_3-17)

1.85 (d, J= 1.2 Hz, 3H, CH_3-18)

1.87 (s, 3H, CH_3-19)

2.14, 2.22 (two singlets, 6H, CH_3CO-2′ + CH_3CO-10)

2.1 - 2.5 (m, 2H, CH_2-14)

2.44 (s, 3H, CH_3CO-4)

4.02 (d, J = 6.2 Hz, 1H, H-3)

4.32, 4.44 (two doublets, J = 8.5 Hz, 2H, CH_2-20)

5.12 (d, J = 5.6 Hz, 1H, H-5)

5.51 (d, J = 3.1 Hz, 1H, H-2′)

5.86 (m, 2H, H-2 + H-7)

5.95 (dd, J = 3.1 Hz, J = 9.1 Hz, 1H, H-3′)

6.07 (dd, J = 5.6 Hz, J = 10.0 Hz, 1H, H-6)

6.23 (m, 2H, H-13 + H-10)

6.89 (d, J = 9.1 Hz, 1H, NH)

7.3 - 8.2 (m, 15H, 3 Ph)

Example 4

7-Deoxy-taxol-6-ene

To a suspension of 2′-acetyl-7-deoxy-taxol-6-ene (21mg, 0.024 mmol) in MeOH : H_2O = 9 : 1 (5mL) was added sodium bicarbonate (5mg, 0.059 mmol). The reaction mixture was stirred for 3hrs at room temperature and then kept for 24hrs at 0°C. The reaction mixture was diluted with water, extracted with ethyl acetate, the organic phase washed with water, brine and dried over sodium sulphate. The crude material was purified by chromatography over silica gel (eluant : n-hexane/ethyl acetate = 1/2) yielding 9.5mg (47%)

of the title compound.

Rf ~ 0.29 (n-hexane/ethyl acetate = 1/1)

FAB-MS:m/z 834, $[M-H]^-$

^1H NMR ($CDCl_3$, 400)

1.15 (s, 3H, CH_3-16)

1.24 (s, 3H, CH_3-17)

1.69 (d, J= 1.5 Hz, 3H, CH_3-18)

1.87 (s, 3H, CH_3-19)

2.23 (s, 3H, CH_3CO-10)

2.2 - 2.5 (m, 2H, CH_2-14)

2.39 (s, 3H, CH_3CO-4)

3.56 (d, J = 4.4 Hz, 1H, OH-2')

4.00 (d, J = 6.5 Hz, 1H, H-3)

4.33 ,4.43 (two doublets, J = 8.5 Hz, 2H,CH_2-20)

4.78 (dd, J = 4.4 Hz, J = 2.5 Hz, 1H, H-2')

5.10 (d, J = 5.6 Hz, 1H, H-5)

5.80 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H, H-3')

5.84 (d, J=6.5 Hz, 1H, H-2)

5.87 (d, J=10.0 Hz, 1H, H-7)

6.06 (dd, J=10.0 Hz, J=5.6 Hz, 1H, H-6)

6.20 (m, 2H, H-10+H-13)

7.02 (d, J=8.8 Hz, 1H, NH)

7.2-8.2 (m, 15H, 3 Ph)

Example 5

7-Deoxy-2'-epi-taxol-6-ene

2'-Acetyl-7-deoxy-taxol-6-ene (139 mg, 0.155 mmole) was

dissolved in a mixture of methanol (10 ml) and methylene chloride (1.5 ml). A 1% methanolic solution of diethylamine was added and the reaction mixure stirred at room temperature for 1 hour.

The reaction mixture was poured into water (100 ml) and extracted with methylene chloride (3 x 30 ml).

The joined organic layers were washed with water, concentrated and purified on preparative silica gel TLC, eluating with hexane/ethylacetate 1:1.

7-Deoxy -taxol-6-ene (78 mg, 60% yield) and the more polar 7-deoxy-2'-epi-taxol-6-ene (mg. 21, 15% yield) was obtained.

Rf ~ 0.18 (n-hexane/ethyl acetate=1/1)

FAB-MS:m/z 834, $[M-H]^-$

^{1}H-NMR (400MHz, $CDCl_3$)

1.12 (s, 3H, 16)

1.19 (s, 3H, 17)

1.49 (d, J=1.2 Hz, 3H, 18)

1.79 (s, 1H, OH-1)

1.84 (s, 1H, 19)

2.1-2.3(m, 2H, CH_2-14)

2.21 (s, 3H, CH_3CO-10)

2.42 (3,3H,CH_3CO-4)

3.44 (bs, 1H, OH-2')

3.98 (d, J=6.6 Hz, 1H, 3)

4.27, 4.43 (two doublets, J=7.9 Hz, 2H, CH_2-20)

4.87 (d, J=3.7, 1H, 2')

5.12 (d, J=5.6 Hz, 1H, 5)

5.75 (dd, J=3.7 Hz, J=8.4 Hz, 1H, 3')

5.81 (d, J=6.6 Hz, 1H, 2)

5.84 (d, J=9.7 Hz, 1H, 7)

6.07 (dd, J=9.7 Hz, J=5.6 Hz, 1H, 6)

6.09 (m, 1H, 13)

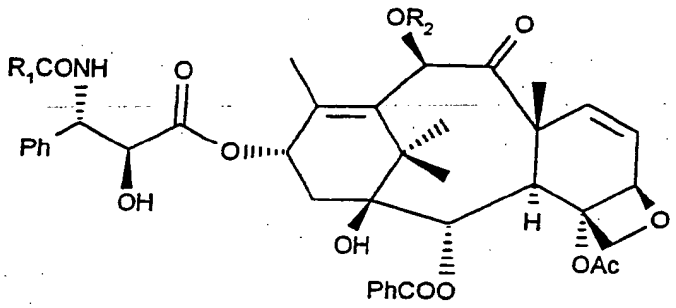
6.16 (s, 1H, 10)

7.09 (d, J=8.4 Hz, 1H, NH-4')

7.2-8.2 (m, 15H, 3-Ø)

CLAIMS

1. A taxane derivative of formula Ia



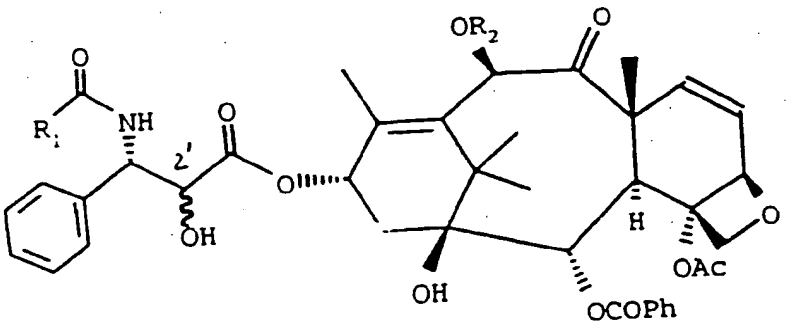
Ia

wherein R_1 represents OR or R wherein R is C_1-C_5 alkyl, C_2-C_5 alkenyl or C_6-C_{10} aryl and R_2 represents H or CH_3CO.

2. A compound according to claim 1, wherein R_1 represents phenyl, tert.butoxy, 1-methyl-1-propenyl or n-pentyl.

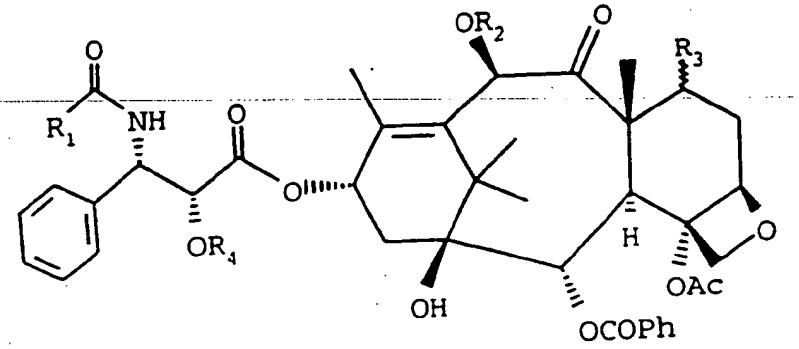
3. A compound according to claim 1, which is 2'-epi-7-deoxy-taxol-6-ene.

4. A process for preparing a taxane derivative of formula I



I

the process comprising carrying out an elimination reaction on a protected taxane derivative of formula II



II

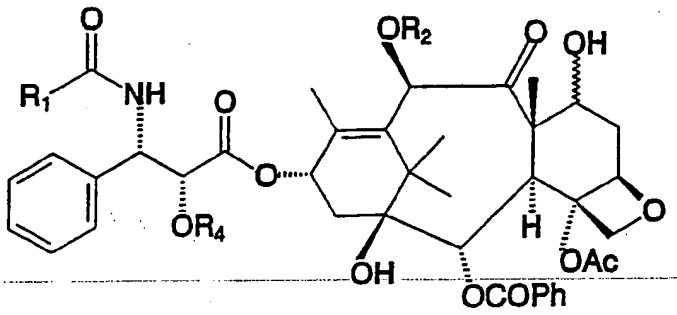
wherein R_1 and R_2 are as defined in claim 1, R_3 is a leaving group and R_4 is a hydroxy protecting group, thereby to form a said taxane derivative of formula I wherein the 2'-hydroxy group carries a said hydroxy protecting group R_4; and carrying out the following steps in any order:

a) separating the resulting isomers which are in the α and β configuration at the 2'-position; and

b) removing the said hydroxy protecting group R_4.

5. A taxane derivative of formula II as defined in claim 4 characterized in that R_3 is CH_3SO_2O or CF_3SO_2O in the α configuration.

6. A process for preparing a taxane derivative of the formula II as defined in claim 5, which process comprises reacting a compound of formula III:



III

wherein R_1, R_2 and R_4 are as defined in claim 4, with a compound of formula IV:

$$CX_3SO_2\text{-}Y \qquad \text{IV}$$

wherein X is H or F and Y is a leaving group.

7. A pharmaceutical composition which comprises, as active ingredient, a compound of the formula Ia or II as defined in claim 1 or 5 and a pharmaceutically acceptable diluent or carrier.

8. A compound of formula Ia or II as defined in claim 1 or 5 for use in a method of treatment of the human or animal body by therapy.

9. A compound as claimed in claim 8 for use as an antitumour agent.

10. A process for preparing a taxane derivative of formula I as defined in claim 4, said process being substantially as hereinbefore described in Examples 3 and 4 taken together or Examples 3 and 5 taken together.

11. A process for preparing a taxane derivative of formula II as defined in claim 5, said process being substantialy as hereinbefore described in Example 2.

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Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

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Relevant Technical Fields

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(ii) Int Cl (Ed.6) C07D 305/14

Search Examiner
P N DAVEY

Date of completion of Search
4 JULY 1995

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE: CAS ONLINE

Documents considered relevant following a search in respect of Claims :-
1-4, 7-9 (IN PART) AND 10

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
P,X	EP 0600517 A1 (BRISTOL-MYERS SQUIBB) 8 June 1994, see eg formula Ia	1 at least
P,X	Tetrahedron Lett. (1994), 35(43), 7893-6	1 at least
P,X	Bioorg. Med. Chem. Lett. (1994), 4(18), 2223-8	1 at least

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).